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BY FACSIMILE ONLY **Fax. 011 49 89 2399-4465**

July 19, 2000

Attention: T. Butkowskyj-Walkiw
International Preliminary Examining Authority
European Patent Office
D-80298 Munich
Germany

Re: PCT/CA99/00311
Applicant: CURRY, Kenneth *et al.*
Our File: 114-149PCT (formerly 379-110PCT)

Dear Sir/Madam:

RESPONSE TO WRITTEN OPINION

This communication is in response to the Written Opinion mailed March 3, 2000.

ITEM V: WITH REGARD TO NOVELTY, INVENTIVE STEP OR INDUSTRIAL APPLICABILITY

Please note that claims 5, 7, 8, 9 and 10 accompanying this response have been amended and claims 11 - 21 have been added. A first set of new claims reflecting the changes with added wording being indicated by the use of underlining and deleted wording being indicated within brackets. The Applicant has also enclosed a second set of said amended claims in final format.

The Examiner states that Claims 1-10 are novel. The Examiner also states that claims 1-10 are

inventive in view of document D1 (PELLICCIARI *et al.*, Assymmetric Synthesis of Enantiomerically pure (2S, 1'S, 2's, 3'R)-phenylcarboxycyclopropylglycine, BIORGANIC & MEDICINAL CHEMISTRY LETTERS, vol 6, no. 18, pages 2243-2246, 1996) which the Examiner considers to be the closest prior art document, indeed, the Examiner states that "in light of this teaching it was not obvious for a skilled person to arrive at the present subject matter." Regarding the Examiner's comments relating to industrial applicability and claim 7 the Applicant elects to amend the claim language after National Phase entry, and when requisitioned.

ITEM VI: CERTAIN DOCUMENTS CITED

The Examiner states that the present application claims priority rights from 17/4/98. The Applicant therefore asserts that the D1 document (PELLICCIARI *et al.*, Assymmetric Synthesis of Enantiomerically pure (2S, 1'S, 2's, 3'R)-phenylcarboxycyclopropylglycine, BIORGANIC & MEDICINAL CHEMISTRY LETTERS, vol 6, no. 18, pages 2243-2246, 1996) does not constitute prior art, as the priority date of this application predates the publication date of D1 document. Nonetheless, the Examiner states that "in light of this teaching it was not obvious for a skilled person to arrive at the present subject matter."

ITEM VII: CERTAIN DEFECTS IN THE INTERNATIONAL APPLICATION

The Examiner states that claim 3 and claim 4 are inconsistent with their dependency on claim 1. The Article 19 amendment, received by the International Bureau on October 28, 1999, corrects for the incorrect definition of R2 in claim 3 and R4 in claim 4.

ITEM VIII: CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION

The Examiner comments that the term "aliphatic" used in claim 1 is too broad in scope and therefore unclear (Art. 6 PCT). The Applicant respectfully argues that the term "aliphatic" would be understood by a worker skilled in the art. The term "aliphatic" has been defined on page 13 of

"Dictionary of Chemistry" by Sybil P. Parker, published by McGraw-Hill as "pertaining to any organic compound of hydrogen and carbon characterized by a straight chain of carbon atoms; three subgroups of such compounds are alkanes, alkenes, and alkynes." The Applicant therefore believes that a worker skilled in the art, having regard to the instant application and the definition given in the above reference, would understand the meaning of the term "aliphatic" used in claim 1.

The Examiner further objects to the terms "the like" and "about" for being in definite and unclear. These terms are not used in the claims and are used in specification only. Therefore the scope of protection sought be the instant application is not affected by the inclusion of such terms.

The Examiner has further pointed out that in claims 5 and 8-10, the definition of the substituents should be included or these claims should be made dependent on claim 1. The Applicants have amended claims 5 and 8-10 to include the definition of a substituents.

REQUEST TO RE-AMEND TITLE

The Applicant was informed, in the International Search Report, that the Authorized Officer had amended the title of the application from "Cubane Analogs with Activity at the Metabotropic Glutamate Receptors" to "Cubane Derivatives as Metabotropic Glutamate Receptor Antagonists and Process for their Preparation." The Applicant respectfully requests that the title be amended to include compounds exhibiting both antagonist and agonist activity. Support for this amendment can be found on page 18 in the paragraph relating to Second Messenger Activity, which clearly explains the procedure for conducting both antagonist and agonist assays. The Applicant therefore requests that the title be amended to read "Cubane Derivatives as Metabotropic Glutamate Receptor Agonists or Antagonists and Process for their Preparation."

AMENDMENTS UNDER PCT ARTICLE 34

The Applicant has amended the specification to correct for typographical and clerical errors as

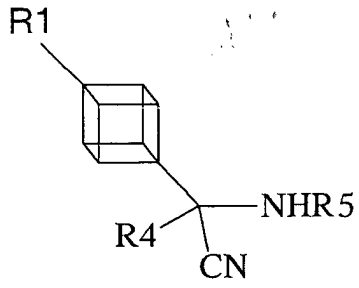
follows:

At page 8, line 7, replace "COOH" with --NH_2--.

At page 8, line 8, after "thioxanthyl", insert -- -CH_2-xanthyl- or -CH_2-thioxanthyl- --.

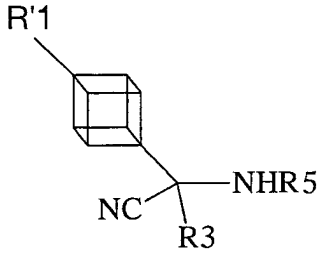
At page 8, line 9, replace "NH_2" with--COOH--.

At page 11, replace "(a) hydrolyzing a compound of formula:



(II)

in which **R1** is as defined above, **R5** represents a hydrogen atom or an acyl group and **R4** has the meaning defined above. Preferred values for **R5** are hydrogen and (2-6C) alkanoyl groups, such as acetyl" with --(a) hydrolyzing a compound of formula (IIa):

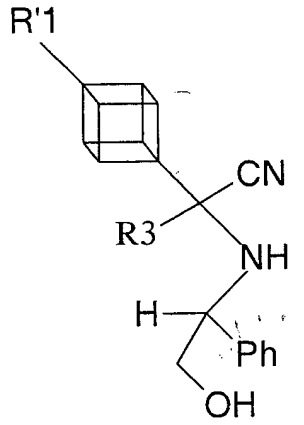


(IIa)

wherein: **R'1** is an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -CH_2-carboxyl, -CH_2-phosphono, -CH_2-phosphino, -CH_2-sulfono, -CH_2-sulfino, -CH_2-borono, -CH_2-tetrazol, -CH_2-isoxazol and higher analogues thereof, or a protected form thereof, **R3** can be H, aliphatic, aromatic or heterocyclic and **R5** represents a hydrogen atom or an acyl group. Preferred values for **R5** are hydrogen and (2-6C)

alkanoyl groups, such as acetyl; or--.

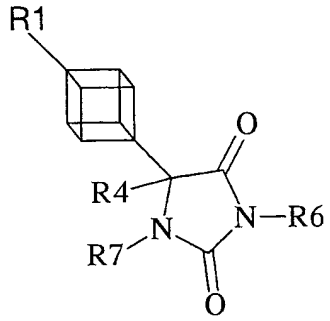
At page 11, after, "Preferred values for **R5** are hydrogen and (2-6C) alkanoyl groups, such as acetyl; or", insert --(b) deprotecting and hydrolyzing a compound of formula (II b)



(IIb)

wherein: **R'1** and **R3** are as defined above; or--.

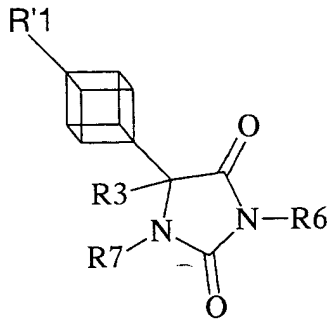
At page 11, replace "(b) hydrolyzing a compound of formula:



(III)

in which **R6** and **R7** each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof; or"

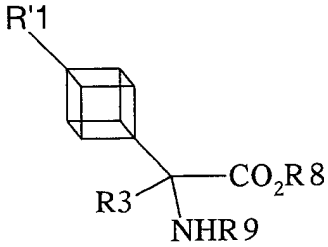
with --(c) hydrolyzing a compound of formula:



(III)

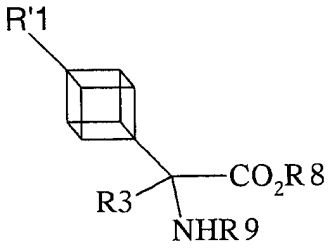
wherein: **R'1** and **R3** has the meaning defined above, **R6** and **R7** each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof; or-- and move the replaced paragraph to new page 11a.

At page 12, replace "(c) deprotecting a compound of formula:



(IV)

in which **R8** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R9** represents a hydrogen atom or a nitrogen protecting group;" with --(d) deprotecting a compound of formula:



(IV)

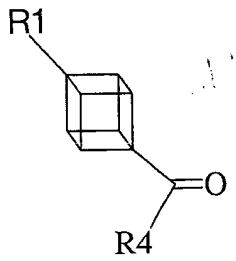
wherein: **R'1** and **R3** has the meaning defined above, **R8** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R9** represents a hydrogen atom or a nitrogen protecting

group;--.

At page 13, line 17, replace "Formula V" with --Formula IV--.

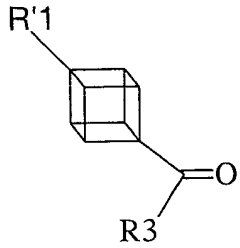
At page 13, line 22, replace "Formula V" with --Formula IV--.

At page 13, replace "The compounds of Formula II may be prepared by reacting a compound of formula:



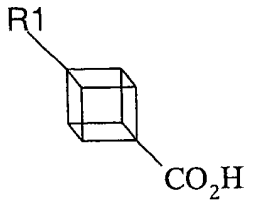
(V) "

with --The compounds of Formula II may be prepared by reacting a compound of formula:



(V) --

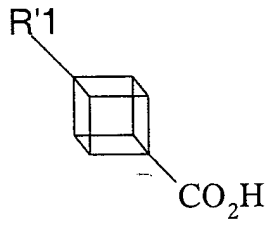
At page 14, replace "The compounds of Formula V can be prepared by reacting a compound of formula:



(VI)

with a chlorinating agent such as thionyl chloride or phosphorous (V) chloride, followed by reaction

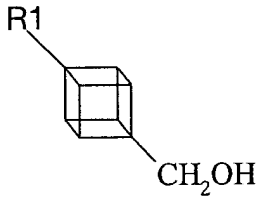
with **R4**X wherein **R4** has the meaning defined above and X is halogen" with --The compounds of Formula V can be prepared by reacting a compound of formula:



(VI)

with a chlorinating agent such as thionyl chloride or phosphorous (V) chloride, followed by reaction with organo copper or organo metal or Grignard reagent derived from **R3**X or by reaction with ethyl hydrogen malonate in the presence of organolithium, wherein **R3** has the meaning defined above and X is halogen--.

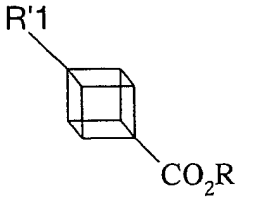
At page 15, replace "The compounds of Formula V can also be prepared by oxidizing a compound of formula



(VII)

under Swern conditions.

The compounds of Formula VI can be prepared from compounds of formula:

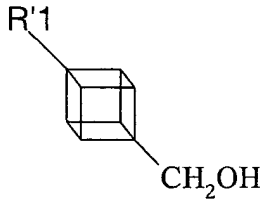


(VIII)

by reduction.

If **R1** is CO_2Me, this compound can be bought commercially. If **R1** is another substituent, the compound of Formula VIII can be made using standard procedures" with --The compounds of

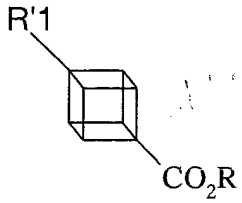
Formula V can also be prepared by oxidizing a compound of formula :



(VII)

under Swern conditions.

The compounds of Formula VI can be prepared from compounds of formula:



(VIII)

by reduction.

When **R'1** is CO_2Me, this compound can be bought commercially. When **R'1** is another substituent, the compound of Formula VIII can be made using standard procedures--.

At page 31, line 26, replace "*Preparation 5*: 4-carbonyl-1-cubanylglycine" with --*Preparation 5*: 4-carboxy-1-cubanylglycine--.

Remarks Relating to Article 34 Amendments

To aid the Examiner in the interpretation of the Article 34 amendments listed above, the Applicant hereby submits the following remarks.

The Applicant voluntarily amends the specification on page 8, to correct for typographical errors in the designation of R2 and R4, as follows. The definition of R_2 as COOH, has been replaced with NH_2 and in the definition of R4 as NH_2, has been replaced with COOH, for reasons of consistency. Support for this amendment can be found throughout the application as filed. For example, on page 7 it is stated that R2 can be a basic group selected from the group consisting of 1° amino, 2° amino,

3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea; and that R4 can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol.

The Applicant further voluntarily amends the specification on page 8, to insert the phrase "-CH_2-thioxanthyl and -CH_2-xanthyl" into the definition of R3. This amendment is supported by Example 3, compound 5, on page 31. Inclusion of the term "-CH_2-xanthyl" can be explained on the basis that having regard to successful synthesis of compound (I), wherein R3 = -CH_2-thioxanthyl, corresponding examples of compound (I), wherein R3 = -CH_2-xanthyl can be prepared by a person skilled in the art.

On page 11, compound II has been renumbered as compound IIa and compound IIb has been inserted. This amendment has been made to clarify the description and to specifically indicate that compound 5, formed in the Example 1, can be an intermediate in the preparation of compound (I). Moreover, this amendment is necessary to encompass the compound formed by reaction of compound (V) with phenylglycinol and TMSCN, as described on page 13 of the specification and on page 31 of the experimental section (preparation 4). This compound does not fall under generic compound (II), shown on original page 11 of the specification as the "R5" moiety of the substituent "–NHR5" was defined as H or (C_2-C_6) alkanoyl group, whereas in the compound formed as described on pages 13 and 30, the R5 substituent attached to -NH group is very specific and was not included in the original general definition of R5 as shown on page 11.

In structural formulae (II), (III) on pages 11 and 39, (IV) on pages 12 and 40 and structural formula (V), on page 13, the given substituent, R4 has been replaced with R3, for reasons of consistency. The typographical nature of the error is obvious in light of the fact that the compounds (II), (III) and (IV) are the intermediate compounds formed in the synthesis of the final compound of formula (I). Hence, under hydrolyzing and deprotection conditions given on pages 11-13, compound (II), (III),

or (IV) should be converted to compound (I). For example: (i) under hydrolyzing conditions, the -CN group of compound (IIa) or (IIb) is converted to -COOH group of compound (I); and under hydrolyzing, and/or deprotecting, conditions, -NHR5 of compound (IIa) and -NH-CH(Ph)CH_2OH group of compound (IIb) are converted to -NH_2 group of compound (I); (ii) under hydrolyzing conditions, the cyclic group of compound (III), containing R6 and R7 as substituents, opens up to -COOH and -NH_2 groups of compound (I); (iii) under deprotection conditions CO_2R8 of compound (IV) becomes -COOH of compound (I) and -NHR9 of compound (IV) becomes -NH_2 of compound (I). In compound (I), COOH is defined as R4 and NH_2 is defined as R2. If the third substituent in the compound (IIa), (IIb), (III) and (IV) is R4, then the compound (I) formed after hydrolyzing or deprotecting these compounds will have one substituent as R2 and two substituents as R4, and R3 will be missing from the desired compound (I). Therefore in order to obtain the desired compound (I) with one substituent as R2, second as R3 and third as R4, the third substituent in compounds (IIa) (IIb), (III) and (IV) should be R3 instead of R4. Further support for this amendment can be found in the schematic representation of the synthetic procedures presented on pages 32 and 33 of the experimental section of the instant application.

On page 13, 4th paragraph, in the phrases "heating the compound of formula V" and "reacting the compound of formula V", the given number "V" has been replaced with number "IV" to correct for a typographical error.

On page 14, the Applicant has replaced the phrase "with R4X, wherein R4 has the meaning defined above and X is halogen or OH" with the phrase "with organocopper, organometal and Grignard reagents, derived from R3X, or by reaction with ethyl hydrogen malonate in the presence of organolithium, wherein R3 has the meaning defined above and X is halogen" to clarify the description. The Applicant believes that this amendment is allowable because a large number of organocopper, organometal and Grignard reagents are commercially available, and these regents can also be easily prepared by a person skilled in the art. Support for the preparation of organocopper reagent from organometallic compound can be found in preparation 3 of example 2 presented on

page 33 of the instant application. Support for the use of ethyl hydrogen malonate can be found in Preparation 1 of Example 3, presented on page 34 of the application on file.

In the given structural formulae for compounds (II), (III), (IV), (V), (VI), (VII), and (VIII), pages the substituent "R1" has been changed to "R'1", to distinguish between the compounds having the protected forms of the group -COOH , as shown in the Examples 2, 3 and 4 in the experimental section of the instant application.

On page 31, the name of the compound in the preparation 5 has been amended, from "4-carbonyl-1-cubanylglycine" to "4-carboxy-1-cubanylglycine", to correct a typographical error. Support for this amendment can be found on page 33, wherein the compound of preparation 5, having similar group at position 4 is named as 4-carboxycubane-1-methylglycine.

The Applicant has also voluntarily amended a number of the claims to better clarify the present invention. Additional claims 11-13 and 18-21 have been submitted to specifically claim the exemplary compounds and the intermediates prepared and described in the application as filed. Additional claims 14-17 have been submitted to claim the use of the compounds of claim 1 and to claim the use of the exemplary compounds prepared and described in the application as filed.

The Applicant asserts that no new matter has been added by way of these amendments and respectfully requests that the Examiner respond to the amended claims and above assertions in a favorable manner.

Respectfully submitted,

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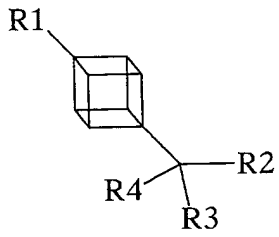
MSS/pt
Encl.

In particular compoun[redacted]wherein the compound of Formula [redacted] selected from the group consisting of:



(I)

wherein:

R1 is COOH
R2 is NH_2
R3 can be H or methyl or xanthyl or thioxanthyl or $-CH_2$-xanthyl or $-CH_2$-thioxanthyl and
R4 is COOH

While all of the compounds of Formula I are believed to demonstrate activity at the metabotropic glutamate receptors (mGluRs), certain groups of Formula I compounds are more preferred for such use.

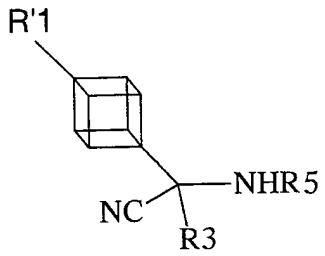
As noted above, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic

According to another aspect, the present invention provides a process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

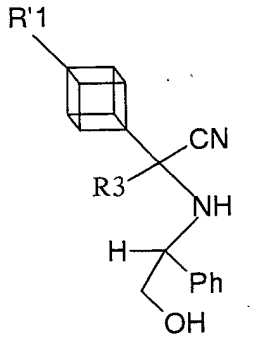
(a) hydrolyzing a compound of formula (IIa):



(IIa)

wherein: **R'1** is an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -CH_2-carboxyl, -CH_2-phosphono, -CH_2-phosphino, -CH_2-sulfono, -CH_2-sulfino, -CH_2-borono, -CH_2-tetrazol, -CH_2-isoxazol and higher analogues thereof, or a protected form thereof, **R3** can be H, aliphatic, aromatic or heterocyclic and **R5** represents a hydrogen atom or an acyl group. Preferred values for **R5** are hydrogen and (2-6C) alkanoyl groups, such as acetyl; or

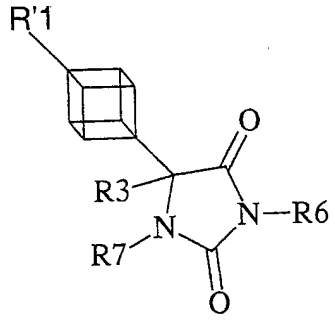
(b) deprotecting and hydrolyzing a compound of formula (II b)



(IIb)

wherein: **R'1** and **R3** are as defined above; or

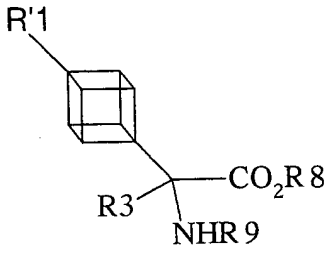
(c) hydrolyzing a compound of formula:



(III)

wherein: **R'1** and **R3** has the meaning defined above, **R6** and **R7** each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof; or

(d) deprotecting a compound of formula:



(IV)

wherein: **R'1** and **R3** has the meaning defined above, **R8** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R9** represents a hydrogen atom or a nitrogen protecting group;

whereafter, if necessary and/or desired:

(i) resolving the compound of Formula I;
(ii) converting the compound of Formula I into a non-toxic metabolically-labile ester or amide thereof;
and/or;
(iii) converting the compound of Formula I or a non-toxic metabolically-labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

The protection of carboxylic acid and amine groups is generally described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxyl protecting groups include alkyl groups such as methyl, ethyl, *t*-butyl and *t*-amyl; aralkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and *t*-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine-protecting groups include acyl groups, such as groups of formula **R9** CO in which **R9** represents (1-6C) alkyl, (3-10C) cycloalkyl, phenyl(1-6C) alkyl, phenyl(1-6C) alkoxy, or a (3-10C) cycloalkoxy, wherein a phenyl group may optionally be substituted by one or two

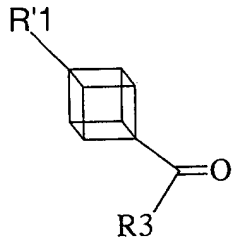
substituents independently selected from amino, hydroxy, nitro, halogeno, (1-6C) alkyl, (1-6C) alkoxy, carboxyl, (1-6C) alkoxycarbonyl, carbamoyl, (1-6C) alkanoylamino, (1-6C) alkylsulphonylamino, phenylsulphonylamino, toluenesulphonylamino, and (1-6C) fluoroalkyl.

The compounds of Formula II are conveniently hydrolyzed in the presence of an acid, such as hydrochloric acid or sulfuric acid, or a base, such as an alkali metal hydroxide, for example sodium hydroxide. The hydrolysis is conveniently performed in an aqueous solvent such as water and at a temperature in the range of 50 to 200 °C.

The compounds of Formula III are conveniently hydrolyzed in the presence of a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline earth metal hydroxide such as barium hydroxide. Suitable reaction media include water. The temperature is conveniently in the range of from 50 to 150 °C.

The compounds of Formula IV may be deprotected by a conventional method. Thus, an alkyl carboxyl protecting group may be removed by hydrolysis. The hydrolysis may conveniently be performed by heating the compound of Formula IV in the presence of either a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline metal hydroxide, such as barium hydroxide, or an acid such as hydrochloric acid. The hydrolysis is conveniently performed at a temperature in the range from 10 to 300 °C. An aralkyl carboxyl protecting group may conveniently be removed by hydrogenolysis. The hydrogenolysis may conveniently be effected by reacting the compound of Formula IV with hydrogen in the presence of a Group VIII metal catalyst, for example a palladium catalyst such as palladium on charcoal. Suitable solvents for the reaction include alcohols such as ethanol. The reaction is conveniently performed at a temperature in the range from 0 to100 °C. An acyl, amine protecting group is also conveniently removed by hydrolysis, for example as described for the removal of an alkyl carboxyl protecting group.

The compounds of Formula II may be prepared by reacting a compound of formula (V):



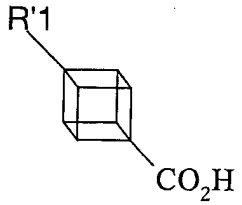
(V)

with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and an ammonium halide, such as ammonium chloride, conveniently in the presence of ultrasound. Thus, the ammonium halide is mixed with chromatography grade alumina in the presence of a suitable diluent such as acetonitrile. The mixture is then irradiated with ultrasound, whereafter the compound of Formula V is added, and the mixture is again irradiated. The alkali metal cyanide is then added, followed by further irradiation with ultrasound.

Individual isomers of compounds of Formula I may be made by reacting a compound of the Formula V with the stereoisomers of the chiral agent (*S*)- and (*R*)-phenylglycinol and a reactive cyanide such as trimethylsilyl cyanide.

The compounds of Formula III may be prepared by reacting a compound of Formula V with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and ammonium carbonate or ammonium carbamate. Convenient solvents include water, dilute ammonium hydroxide, alcohols such as methanol, aqueous methanol and aqueous ethanol. Conveniently the reaction is performed at a temperature in the range of from 10 to 150 °C. If desired, the compounds of Formula III may then be alkylated, for example using an appropriate compound of formula **R6** Cl and/or **R7** Cl.

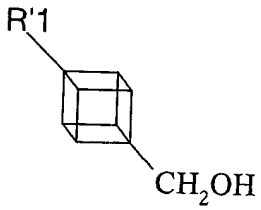
The compounds of Formula V can be prepared by reacting a compound of formula:



(VI)

with a chlorinating agent such as thionyl chloride or phosphorous (V) chloride, followed by reaction with organo copper or organo metal or Grignard reagent derived from **R3** X or by reaction with ethyl hydrogen malonate in the presence of organolithium, wherein **R3** has the meaning defined above and X is halogen.

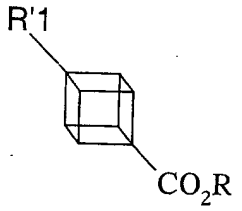
The compounds of Formula V can also be prepared by oxidizing a compound of formula



(VII)

under Swern conditions.

The compounds of Formula VI can be prepared from compounds of formula:



(VIII)

by reduction.

When **R'1** is CO_2Me, this compound can be bought commercially. When **R'1** is another substituent, the compound of Formula VIII can be made using standard procedures.

Many of the intermediates described herein, for example the compounds of Formula II, III and IV are believed to be novel, and are provided as further aspects of the invention.

The Formula I compounds of the present invention are agonists or antagonists at certain metabotropic excitatory amino acid receptors (mGluRs). Therefore, another aspect of the present invention is a method of affecting mGluRs in mammals, which comprises administering to a mammal requiring modulated excitatory amino acid neurotransmission a pharmacologically-effective amount of a compound of Formula I. The term "pharmacologically-effective amount" is used to represent an amount of the compound of the invention that is capable of affecting the mGluRs. By affecting, a compound of the invention is acting as an agonist or antagonist. When a compound of the

allowed to come to room temperature. Water (3 mL) is added and stirred for 30 min, potassium carbonate (0.85 g) is added and the solution extracted with Et_2O. The organic phase is dried over magnesium sulfate and evaporated to give the alcohol (3) 0.46 g (100%) m.p. 83-85 °C. ^1H NMR(200 MHz, solvent) δ: 1.58 (s, 1H), 3.62 (s, 3H), 3.72 (s, 2H), 3.81 (m, 3H), 4.1 (m, 3H).

Preparation 3: 4-methoxycarbonyl-1-(formyl) cubane

DMSO (0.7 mL, 9.68 mmol) is added to oxalyl chloride (0.42 mL, 4.84 mmol) in 12 mL of CH_2Cl_2 at -78 °C. The alcohol (3) (0.46 g, 2.42 mmol) in 3 mL CH_2Cl_2 is added and stirred at –78 °C for 1.5 h. Triethylamine (2.0 mL, 14.4 mmol) is added and the mixture is allowed to come to 0°C. Saturated ammonium chloride solution is added and the phases separated, the aqueous layer is extracted with CH_2Cl_2 and the combined organic layers are dried ($MgSO_4$), then evaporated to give crude product which is purified by flash chromatography (1:1 hexanes:diethyl ether) to give 0.35 g (76%) of pure product (4). ^1H NMR (200 MHz, solvent) δ: 3.7 (s, 3H), 4.2 (m, 3H), 4.32 (m, 3H), 9.72 (s, 1H).

Preparation 4: 4-methoxycarbony-1-[2'-hydroxy-1'-phenylethyl] methylnitrilecubane

(*R*)-phenylglycinol (257 mg, 1.87 mmol) is added to a solution of the aldehyde (4) (0.35 g, 1.84 mmol) in 14 mL of methanol. The solution is cooled to 0 °C and TMSCN (0.49 mL, 3.68 mmol) is added and the mixture stirred at 0 °C overnight. Evaporation of the solvent leaves a residue which is purified by chromatography (diethyl ether:hexanes, 3:1) to give 0.48 g (77%) of pure product (5). ^1H NMR ($CDCl_3$) δ: 2.23 (s, 1H), 2.6 (br, 1H), 3.5-3.75 (m, 2H), 3.7 (s, 3H), 3.9 (m, 3H), 4.11 (dd, 1H), 4.2 (m, 3H), 7.3 (s, 5H).

Preparation 5: 4-carboxy-1-cubanylglycine

Lead acetate (0.69 g, 1.57 mmol) is added to a stirred solution of nitrile (5) (0.48 g, 1.42 mmol) in dry methanol/dichloromethane 1:1 (12 mL). After 10 min 10 mL of water is added and the suspension filtered through celite. The organic layer is dried and evaporated to give the crude imine. The crude imine is refluxed with 6N HCl (30 mL) for 6 hr. The solution is evaporated to dryness and placed on anion exchange resin, eluting with 1N acetic acid to yield the product (6). mp. 241 ºC (dec.) ^1H NMR (D_2O) δ 3.96 (s, 1H), 4.01 (m, 3H), 4.14 (m, 3H).